

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19372 A1

(51) International Patent Classification⁷: A61K 31/565, 31/66, 9/08, A61P 35/00, A61K 47/18

(21) International Application Number: PCT/EP00/08983

(22) International Filing Date: 13 September 2000 (13.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 9921960.2 16 September 1999 (16.09.1999) GB

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/19372 A1

(54) Title: FORMULATIONS FOR PARENTERAL USE OF ESTRAMUSTINE PHOSPHATE AND AMINO ACIDS

(57) Abstract: A pharmaceutical formulations which comprises a parenterally acceptable carrier or diluent and estramustine phosphate and a basic amino acid. The formulation can be administered according to a combined chemotherapy regimen in association with one or more chemotherapeutic agents. The formulation also enables the estramustine phosphate to be administered with no side effects at the site of injection.

**FORMULATIONS FOR PARENTERAL USE OF ESTRAMUSTINE PHOSPHATE
AND AMINO ACIDS**

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The present invention relates to pharmaceutical formulations of estramustine phosphate for parenteral use and, more particularly, to formulations of estramustine phosphate for parenteral use further comprising basic amino acids.

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Estramustine phosphate (The Merck Index, XII Ed., No. 3749, 1996) is an estradiol-17 β -phosphate derivative widely known in the art as antitumor agent, currently used in the treatment of advanced adenocarcinoma of the prostate.

15 The drug is usually administered orally, preferably at a dose of 10-15 mg/kg/day. Intravenous administration, however, is also adopted in some particular cases.

20 For example, initial intravenous administration of estramustine phosphate, followed by oral administration, has been reported at dosages paralleling the oral administration for the drug, i.e. 300-600 mg daily given intravenously and usually repetitively over for several consecutive days (see, for a reference, British Journal of 25 Urology, 1977, 49, 73-79; J. Urol. 108:303-306, 1972; Eur. Clin. Pharmacol. 26(1), 113-119, 1984; Eur. Urol. 1990, 17, 216-218).

30 Estramustine phosphate as well as other well-known cytotoxic compounds used in antitumor therapy are known to cause, or potentially cause, vascular damages at the site of injection when parenterally, in particular intravenously, administered.

35 As an example, studies in patients treated with estramustine phosphate administered as a slow intravenous injection or as a bolus, at 300 mg/day, revealed

19. A product according to claim 17 or 18 wherein the chemotherapeutic agent is selected from the group consisting of taxane derivatives such as paclitaxel and docetaxel; camptothecin and derivatives thereof such as 5 CPT-11 and 9-amino-camptothecin; anthracycline derivatives such as doxorubicin, epirubicin, idarubicin, daunorubicin, alkycycline (4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-daunorubicin; internal code PNU 159548); etoposide; navelbine; vinblastine; platinum derivatives 10 such as carboplatin and cisplatin; angiogenesis inhibitors such as Sugen SU-5416 and Sugen SU-6668; optionally within liposomal formulations thereof.

20. A product according to claim 17 for intravenous use.

15 21. A product according to claim 17 for use in the treatment of prostate cancer, breast cancer, melanoma, lung cancer, pancreatic cancer, colorectal cancer, ovarian cancer or cancer of the brain.

20 22. A formulation as defined in claim 13 for use in suppressing or reducing the side-effects associated with the intravenous administration of estramustine phosphate and pharmaceutically acceptable salts thereof.

25 23. A formulation according to claim 22 wherein the side effects comprise ulcerative lesions and thrombophlebitis at the site of injection.

30 24. A product which comprises estramustine phosphate in lyophilised form and a physiological solution for parenteral use containing a basic amino acid.

35 25. Use, in the manufacture of a medicament for parenteral administration, of estramustine phosphate and a basic amino acid.

26. Use according to claim 25 wherein the medicament is for intravenous administration.

5 **27.** A pharmaceutical formulation which comprises a parenterally acceptable carrier or diluent, an antineoplastic agent known to cause ulcerative damages at the site of injection upon intravenous administration, and arginine or a pharmaceutically acceptable salt thereof.

10 **28.** A formulation according to claim 27 wherein the antineoplastic agent is selected from the group consisting of anthracycline derivatives such as doxorubicin, epirubicin, idarubicin, daunorubicin and alkycycline (4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-15 daunorubicin; internal code PNU 159548); and angiogenesis inhibitors such as Sugen SU-5416 and Sugen SU-6668.

20 **29.** Use of arginine, or of pharmaceutically acceptable salts thereof, in the preparation of a medicament for the treatment and prevention of side-effects associated with the intravenous administration of antineoplastic agents.

25 **30.** Use according to claim 29 wherein the side-effects comprise ulcerative lesions and thrombophlebitis at the site of injection.

30 **31.** Use according to claim 29 wherein the antineoplastic agent is selected from the group consisting of estramustine phosphate; anthracycline derivatives such as doxorubicin, epirubicin, idarubicin, daunorubicin and alkycycline (4-demethoxy-3'-deamino-3'-aziridinyl-4'-methylsulfonyl-15 daunorubicin; internal code PNU 159548); and angiogenesis inhibitors such as Sugen SU-5416 and Sugen SU-6668.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08983

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/565	A61K31/66	A61K9/08	A61P35/00	A61K47/18
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 785 976 A (K.WESTESEN ET AL.) 28 July 1998 (1998-07-28) claims 1,4,5,8-11,14,15,17,18,20 column 15, line 15 - line 17 column 15, line 32 - line 33 --- WO 00 59475 A (LIPOCINE INC.,U.S.A.) 12 October 2000 (2000-10-12) claims 1-4,8,19,48-50,57-59,61,63,65,67-78,85-90 claims 110,112-115 page 13, line 24 - line 27 --- -/--	1,8,9, 13,25,26
E		1,8,13, 25,26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

19 January 2001

Date of mailing of the international search report

29/01/2001

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INTERNATIONAL SEARCH REPORT

Intern. ial Application No

PCT/EP 00/08983

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 807 572 A (S. KIM ET AL.) 15 September 1998 (1998-09-15) claims 1,3,25-39 column 5, line 39 - line 41 column 6, line 58 -column 7, line 3 column 7, line 41 column 7, line 60 - line 67 table 1 ----	27-31
A	EP 0 612 530 A (SNOW BRAND MILK PRODUCTS CO. LTD.,JP) 31 August 1994 (1994-08-31) claims 1-4 table 4 ----	27-31

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Information on patent family members

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